EXHIBIT A

Effect of early treatment with fluvoxamine on risk of emergency care and hospitalisation among patients with COVID-19: the TOGETHER randomised, platform clinical trial

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Summary

Background Recent evidence indicates a potential therapeutic role of fluvoxamine for COVID-19. In the TOGETHER trial for acutely symptomatic patients with COVID-19, we aimed to assess the efficacy of fluvoxamine versus placebo in preventing hospitalisation defined as either retention in a COVID-19 emergency setting or transfer to a tertiary hospital due to COVID-19.

Methods This placebo-controlled, randomised, adaptive platform trial done among high-risk symptomatic Brazilian adults confirmed positive for SARS-CoV-2 included eligible patients from 11 clinical sites in Brazil with a known risk factor for progression to severe disease. Patients were randomly assigned (1:1) to either fluvoxamine (100 mg twice daily for 10 days) or placebo (or other treatment groups not reported here). The trial team, site staff, and patients were masked to treatment allocation. Our primary outcome was a composite endpoint of hospitalisation defined as either retention in a COVID-19 emergency setting or transfer to tertiary hospital due to COVID-19 up to 28 days post-random assignment on the basis of intention to treat. Modified intention to treat explored patients receiving at least 24 h of treatment before a primary outcome event and per-protocol analysis explored patients with a high level adherence (>80%). We used a Bayesian analytic framework to establish the effects along with probability of success of intervention compared with placebo. The trial is registered at ClinicalTrials.gov (NCT04727424) and is ongoing.

Findings The study team screened 9803 potential participants for this trial. The trial was initiated on June 2, 2020, with the current protocol reporting randomisation to fluvoxamine from Jan 20 to Aug 5, 2021, when the trial arms were stopped for superiority. 741 patients were allocated to fluvoxamine and 756 to placebo. The average age of participants was 50 years (range 18–102 years); 58% were female. The proportion of patients observed in a COVID-19 emergency setting for more than 6 h or transferred to a teritary hospital due to COVID-19 was lower for the fluvoxamine group compared with placebo (79 [11%] of 741 *vs* 119 [16%] of 756; relative risk [RR] 0·68; 95% Bayesian credible interval [95% BCI]: 0·52–0·88), with a probability of superiority of 99·8% surpassing the prespecified superiority threshold of 97·6% (risk difference 5·0%). Of the composite primary outcome events, 87% were hospitalisations. Findings for the primary outcome were similar for the modified intention-to-treat analysis (RR 0·69, 95% BCI 0·53–0·90) and larger in the per-protocol analysis (RR 0·34, 95% BCI, 0·21–0·54). There were 17 deaths in the fluvoxamine group and 25 deaths in the placebo group in the primary intention-to-treat analysis (odds ratio [OR] 0·68, 95% CI: 0·36–1·27). There was one death in the fluvoxamine group and 12 in the placebo group for the per-protocol population (OR 0·09; 95% CI 0·01–0·47). We found no significant differences in number of treatment emergent adverse events among patients in the fluvoxamine and placebo groups.

Interpretation Treatment with fluvoxamine (100 mg twice daily for 10 days) among high-risk outpatients with early diagnosed COVID-19 reduced the need for hospitalisation defined as retention in a COVID-19 emergency setting or transfer to a tertiary hospital.

Funding FastGrants and The Rainwater Charitable Foundation.

Introduction

Although safe and effective vaccines for COVID-19 have been developed and distributed, there remain, particularly in low resource settings, major challenges regarding their production, allocation, and affordability.[1] Identifying inexpensive, widely available, and effective therapies against COVID-19 is, therefore, of great importance. In particular, repurposing existing medicines

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See Online for appendix 2

Research in context

Evidence before this study
A search of PubMed on Sept 10, 2021 by means of the following search terms "(randomized OR trial) AND (fluvoxamine OR antidepressants OR selective serotonin reuptake inhibitors OR SSRIs) AND (COVID* OR SARS-CoV-2 OR SARS-CoV)", with no date or language restrictions identified one observational study that reported a significant association between antidepressant use and reduced risk of intubation or death (hazard ratio 0·56; 95% CI 0·43–0·73, p<0·001) and one randomised clinical trial that reported that adult outpatients with symptomatic COVID-19, treated with fluvoxamine, compared with placebo, had a lower likelihood of clinical deterioration over 15 days. In this preliminary randomised trial, 152 participants were randomly assigned to receive 100 mg of fluvoxamine (n=80) or placebo (n=72) three times daily for 15 days; the primary endpoint was clinical deterioration within 15 days of randomisation defined by meeting criteria of shortness of breath, hospitalisation for shortness of breath, pneumonia and oxygen saturation less than 92%, or need for supplemental oxygen to achieve oxygen saturation of 92% or greater.

Added value of this study
TOGETHER is the largest randomised trial to assess the effectiveness of fluvoxamine for patients with COVID-19 in the community. Compared with placebo, patients randomly assigned to fluvoxamine had a lower risk of hospitalisation defined as either retention in a COVID-19 emergency setting or transfer to a tertiary hospital due to COVID-19.

Implications of all the available evidence
There are few effective therapies for patients with COVID-19 in the community. Results provide compelling evidence of fluvoxamine's benefit in reducing acute morbidity from COVID-19 illness.

that are widely available and with well understood safety profiles, has particular appeal.[2]

Fluvoxamine is a selective serotonin reuptake inhibitor (SSRI) and a σ-1 receptor (S1R) agonist.[3] There are several potential mechanisms for fluvoxamine in treatment of COVID-19 illness, including anti-inflammatory and possible antiviral effects.[4] A small placebo-controlled, randomised trial has raised the possibility that fluvoxamine might reduce the risk of clinical deterioration in outpatients with COVID-19, suggesting the need for larger randomised, placebo-controlled studies.[5,6]

To evaluate the efficacy of fluvoxamine to prevent progression of COVID-19 and hospitalisation among outpatients with laboratory-documented SARS-CoV-2, we did a randomised, placebo-controlled, adaptive platform trial in Minas Gerais, Brazil. This flexible platform trial design allows for additional agents to be added and tested with standardised operating procedures outlined in a single overarching master protocol.[7,8] Among eight different interventions evaluated in this platform trial, we report here on the clinical evaluation of fluvoxamine by means of a concurrent placebo control group.

Methods
Study design
The TOGETHER trial is a randomised, adaptive platform trial to investigate the efficacy of repurposed treatments for COVID-19 disease among high-risk adult outpatients.[9] The trial was designed and done in partnership with local public health authorities from 11 participating cities in Brazil to simultaneously test potential treatments for early disease by means of a master protocol. A master protocol defines prospective decision criteria for discontinuing interventions for futility, stopping because of superiority against placebo, or adding new interventions. Interventions evaluated in the TOGETHER

trial, thus far, include, hydroxychloroquine (protocol 1), lopinavir–ritonavir (protocol 1),[10] metformin, ivermectin, fluvoxamine, doxasozin, and pegylated interferon lambda versus matching placebos (protocol 2). The TOGETHER trial is centrally coordinated by Platform Life Sciences (Vancouver, Canada) with local implementation provided by Cardresearch (Belo Horizonte, Brazil). Statistical analyses were done by Cytel (Waltham, MA, USA).

The trial complies with the International Conference of Harmonization—Good Clinical Practices as well as local regulatory requirements. It was approved for research ethics by local and national ethics boards in Brazil (CONEP CAAE: 41174620.0.1001.5120, approval letter 5.501.284) and the Hamilton Integrated Research Ethics Board (approval letter 13390) in Canada. The full protocol and statistical analysis plan have previously been published,[9] and additional details are in appendix 2 (p 2). The adaptive designs Consolidated Standards of Reporting Trials extension statement guided this trial report.[10,11] An independent data safety monitoring committee (DSMC) provided trial oversight.

Participants
The cities and investigators of the 11 clinical sites in Brazil who participated in the trial are listed in appendix 2 (p 3). Local investigators, in partnership with local public health authorities, recruited participants at community health facilities (emergency settings, influenza-symptom referral centres, or primary care community centres). We used several community outreach strategies including physical and social media as per local public health authorities, in order to create awareness of the trial.

On presentation to one of the trial outpatient care clinics, local investigators screened potential participants to identify those who met the eligibility criteria. The

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key inclusion criteria were patients older than 18 years, presenting to an outpatient care setting with an acute clinical condition consistent with COVID-19 and symptoms beginning within 7 days of the screening date, or positive rapid test for SARS-CoV-2 antigen done at the time of screening or patient with positive SARS-CoV-2 diagnostic test within 7 days of symptom onset. Eligible patients also had at least one additional criterion for high risk: diabetes; systemic arterial hypertension requiring at least one oral medication for treatment; known cardiovascular disease (heart failure, congenital heart disease, valve disease, coronary artery disease, cardiomyopathies being treated, clinically manifested heart disease and with clinical repercussion); symptomatic lung disease or treatment for such (emphysema, fibrosing diseases); symptomatic asthma requiring chronic use of agents to control symptoms; smoking; obesity, defined as body-mass index greater than 30 kg/m² (weight and height information provided by the patient); having had a transplant; stage IV chronic kidney disease or on dialysis; immunosuppression or use of corticosteroid therapy (equivalent to at least 10 mg of prednisone per day) or immunosuppressive therapy; history of cancer in the last 0·5 years or undergoing current cancer treatment or aged 50 years or older; and unvaccinated status.

Patients who met any of the following key criteria were excluded from the trial: diagnostic examination for SARS-CoV-2 negative associated with acute flu-like symptoms (patients with negative test taken early and becoming positive a few days later were eligible, if they were less than 7 days after the onset of flu-like symptoms); acute respiratory condition compatible with COVID-19 treated in primary care and previously requiring hospitalisation; acute respiratory condition owing to other causes; received vaccination for SARS-CoV-2; dyspnoea secondary to other acute and chronic respiratory causes or infections (eg, decompensated chronic obstructive pulmonary disease, acute bronchitis, pneumonia, primary pulmonary arterial hypertension); current use of SSRIs (use of other serotonin reuptake inhibitors were not excluded); uncontrolled psychiatric disorders or suicidal ideation; inability or unwillingness to follow research guidelines and procedures. A full list of exclusion criteria is provided in the trial protocol.

If a patient met the aforementioned eligibility criteria, study personnel obtained written informed consent. After obtaining informed consent a rapid antigen test for COVID-19 (Panbio, Abbott Laboratories Jena, Jena, Germany) and a pregnancy test for women of childbearing age were done. If the COVID-19 test was negative or if the pregnancy test was positive, the participant was not included in the trial. After informed consent, study personnel collected the following data before randomisation: demographics, medical history, concomitant medications, comorbidities, exposure to index case information, WHO clinical worsening scale, and the patient-reported outcomes measurement information (PROMIS) Global Health Scale.

Randomisation and masking

Participants were randomly assigned by means of a centralised core randomisation process handled by an independent unmasked pharmacist who was not aware of any protocol-related procedures and contracted specifically for this process. Sites requested randomisation by text message to the pharmacist at the coordinating centre. This maintained concealment of allocation. Patients were randomly assigned (1:1) by means of a block randomisation procedure for each participating site, stratified by age (<50 years or ≥50 years). The trial team, site staff, and patients were masked to treatment allocation. The active drugs and the placebo pills were packaged in identically shaped bottles and labelled with alphabet letters corresponding to the active group or placebo group. Only the third-party pharmacist responsible for releasing the randomisation was aware of which letter was associated with which drug or placebo. As this is a multiarm trial and all active interventions have a matching inert placebo, the matching placebo represents the proportion of the control group for the number of arms in the trial at any given time.

Procedures

All participants received usual standard care for COVID-19 provided by health-care professionals at public health facilities. Patients were randomly assigned to fluvoxamine (Luvox, Abbott) at a dose of 100 mg twice a day for 10 days or corresponding placebo starting directly after randomisation (day 1). Research personnel provided participants with a welcome video, which gave information on the trial, study drug, adverse events, and follow-up procedures. Clinicians providing usual care in public health facilities typically focus on the management of symptoms and provide antipyretics or recommend antibiotics only if they suspect bacterial pneumonia.

Study personnel collected outcome data on days 1, 2, 3, 4, 5, 7, 10, 14, and 28 in person or via telephone contact or social media applications using video-teleconferencing. We collected outcome data irrespective of whether participants took study medication. In case of adverse events, unscheduled visits (during the treatment period) outside of clinical care could occur at any time.

Considering the transmissible characteristics of SARS-CoV-2 and the isolation recommendations of positive individuals, we collected few vital sign data. Cardiac safety was assessed by means of a six-lead electrocardiogram (Kardiamobile, Mountain View, CA, USA) at the baseline visit. The digital recordings were deidentified and transferred to a central facility (Cardresearch, Belo Horizonte, Brazil) for reading. Oxygen status was assessed by means of a pulse oximeter for non-invasive arterial oxygen saturation and pulse (Jumper Medical Equipment, Shenzhen, China), and temperature by
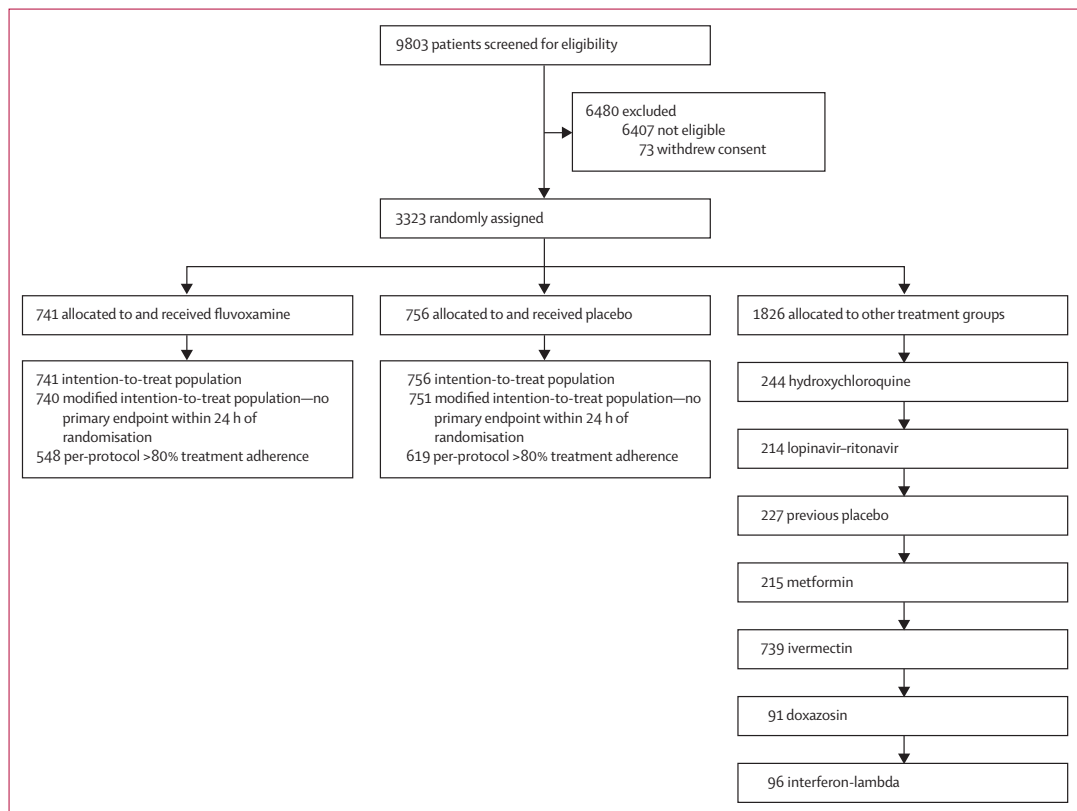
Figure 1: Trial profile

means of a standard digital oral thermometer administered by research personnel. Mid-turbinate nasal swab kits and sterile recipient storage were provided for collection of nasopharyngeal swab or sputum–saliva. Nasal swabs for PCR testing was completed on the first quarter of participants enrolled in the trial on days 3 and 7. Viral clearance was assessed to establish whether active drugs showed any antiviral effects.

All serious and non-serious adverse events were reported to study personnel as per local regulatory requirements. Reportable adverse events included serious adverse events, adverse events resulting in study medication discontinuation, and adverse events assessed as possibly related to study medication.

Outcomes

Our primary outcome was a composite endpoint of medical admission to a hospital setting due to COVID-19-related illness defined as COVID-19 emergency setting visits with participants remaining under observation for more than 6 h or referral to further hospitalisation due to the progression of COVID-19 within 28 days of randomisation. Because many patients who would ordinarily have been hospitalised were prevented from admission due to hospital over-capacity during peak waves, the composite endpoint addresses both hospitalisation and a proxy for hospitalisation, retention in a COVID-19 emergency hospital setting. This region of Brazil implemented hospital-like services in the emergency settings with 50–80 bed units providing services including multiday stays, oxygenation, and mechanical ventilation. The 6 h threshold referred only to periods of time recommended for observation by a clinician and does not include waiting times. Key secondary outcomes include viral clearance, time to clinical improvement, number of days with respiratory symptoms, time to hospitalisation for any cause or due to COVID-19 progression, all-cause mortality and time to death from any causes, WHO clinical worsening scale score, days in hospital and on ventilator and adverse events, adverse reactions to the study medications, and the proportion of participants who are non-adherent with the study drugs. All secondary outcomes were assessed up to 28 days following randomisation.

Statistical analysis

The Adaptive Design Protocol and the Master Statistical Analysis Plan provide details of sample size calculation

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and statistical analysis.[9] This trial is adaptive and applies sample size reassessment approaches. To plan for each arm, we assumed a minimum clinical utility of 37·5% (relative risk reduction) to achieve 80% power with 0·05 two-sided type 1 error for a pairwise comparison against the placebo assuming a control event rate of 15%. This resulted in an initial plan to recruit 681 participants per arm. The statistical team did planned interim analyses. Stopping thresholds for futility were established if the posterior probability of superiority was less than 40% at interim analysis. An arm could be stopped for superiority if the posterior probability of superiority met the threshold of 97·6%.

Baseline characteristics are reported as count (%) or median and IQR for continuous variables. We applied a Bayesian framework for our primary outcome analysis and a frequentist approach for all sensitivity analyses and secondary outcomes. Bayesian analysis allows us to report the posterior probability of treatment efficacy at the end of the trial, independently of the decisions made along the way. Posterior efficacy of fluvoxamine for the primary outcome is calculated by means of the beta-binomial model for event rates, as detailed in the appendix of the statistical analysis plan,[12] assuming informed priors on the basis of observational data for both placebo and fluvoxamine, for both intention-to-treat and per-protocol analyses (defined as taking >80% of possible doses). Modified intention to treat (mITT) was defined as receiving treatment for at least 24 h before a primary outcome. We accounted for any temporal changes in event rates by means of only the concurrent randomised population. We assessed subgroup effects according to the preplanned statistical analysis plan. We calculated the number needed to treat.

Secondary outcomes were assessed by means of a prespecified frequentist approach. For viral clearance we fitted a longitudinal, mixed-effect logistic regression model with a treatment and time interaction term for binary patient outcomes (COVID-19 positive–negative) reported on day 3 and 7 from randomisation, with subject random effect. We assessed time-to-event outcomes using Cox proportional hazard models and binary outcomes using logistic regression. Model assumptions were evaluated by testing for proportionality. We did a subgroup analysis and reported p values for the interactions. Per-protocol analyses were considered sensitivity analyses to assess the robustness of the results. We followed the statistical analysis plan and provided a post-hoc analysis where requested by reviewers. All analyses were done by means of R version 4.0.3. Full details of the statistical analysis plan can be found in the Open Science Framework under Data Section.

A data and safety monitoring committee provided independent oversight for this trial. We planned a fourth and final interim analysis of the fluvoxamine group based on data up to Aug 2, 2021. Herein, we present

	Fluvoxamine (n=741)	Placebo (n=756)
Sex		
Female	409 (55%)	453 (60%)
Male	332 (45%)	303 (40%)
Race		
Mixed race*	709 (96%)	719 (95%)
White	6 (1%)	6 (1%)
Black or African American	5 (1%)	5 (1%)
Unknown	21 (3%)	26 (3%)
Age, years		
<50	379 (51%)	368 (49%)
≥50	327 (44%)	328 (43%)
Unspecified	46 (6%)	49 (6%)
Age descriptive statistics		
Median (IQR)	50 (39–56)	49 (38–56)
Body-mass index		
<30 kg/m²	355 (48%)	373 (49%)
≥30 kg/m²	376 (51%)	375 (50%)
Unspecified	10 (1%)	8 (1%)
Time since onset of symptoms, days		
0–3	328 (44%)	310 (41%)
4–7	239 (32%)	267 (35%)
Unspecified	174 (23%)	179 (24%)
Risk factors		
Chronic cardiac disease	9 (1%)	7 (1%)
Uncontrolled hypertension	106 (14%)	88 (12%)
Chronic pulmonary disease	6 (1%)	3 (<1%)
Asthma	12 (2%)	16 (2%)
Chronic kidney disease	2 (<1%)	2 (<1%)
Rheumatological disorder	1 (<1%)	0
Chronic neurological disorder	8 (1%)	6 (1%)
Type 1 diabetes	25 (3%)	22 (3%)
Type 2 diabetes	104 (14%)	92 (12%)
Autoimmune disease	0	2 (<1%)
Any other risk factor(s) or comorbidities	25 (3%)	24 (3%)

Data are n (%). *Self-identified as someone with mixed ancestry.

Table 1: **Patient characteristics by treatment allocation in the TOGETHER trial**

follow-up of all patients up to Sept 9, 2021. The trial is registered at ClinicalTrials.gov (NCT04727424).

Role of the funding source
The funders of the study had no role in the study design, data collection, data analysis, data interpretation, writing of the report, or decision to submit for publication. The executive committee take responsibility for the integrity of the data and the accuracy of the data analysis. The trial executive committee oversaw all aspects of trial conduct, completeness, data accuracy and adherence of trial conduct to the protocol and the committee vouch for the accuracy and completeness of the data and for fidelity to the protocol.

For the **Open Science Framework** see https://www.doi.org/10.17605/OSF.IO/EG37X

Articles

Results

We have screened 9803 potential participants for inclusion in this trial to date. The TOGETHER trial enrolled its first participant on June 2, 2020 and enrolment into the fluvoxamine group began on Jan 20, 2021. As the trial is ongoing, herein we provide descriptive summaries of only those randomly assigned to fluvoxamine and its concurrent control. By

Aug 5, 2021, 1497 recruited participants were randomly assigned to fluvoxamine (n=741) or placebo (n=756), and 1826 were randomly assigned to other treatment groups (figure 1). Herein, we present data on all patients completing 28 days of follow-up as of Sept 9, 2021. The median age was 50 years (range 18–102) and 862 (58%) were women (table 1). Most participants self-identified as mixed race 1428 (95%), 12 (1%) as white, 10 (1%) as black or African heritage, the rest self-identified as unknown 47 (3%). With respect to covariates of age, body-mass index, and comorbidities, the groups were generally well balanced (table 1). The mean number of days with symptoms before randomisation was 3·8 days (SD 1·87).

All patients accessed care via a COVID-19 emergency setting. There were a total of 180 patients in the fluvoxamine group and 251 patients in the placebo group who had any interaction with a COVID-19 emergency setting. The relative risk (RR) for ever visiting a COVID-19 emergency setting was 0·73 (95% CI 0·62–0·88).

	Intention-to-treat analysis			Modified intention-to-treat analysis		
	N	n (%)	Relative risk (95% BCI)	N	n (%)	Relative risk (95% BCI)
Fluvoxamine	741	79 (11%)	0·68 (0·52–0·88)	740	78 (11%)	0·69 (0·53–0·90)
Placebo	756	119 (16%)	1 (ref)	752	115 (15%)	1 (ref)

BCI=Bayesian credible interval.

Table 2: Proportion of primary outcome events and relative risk of hospitalisation defined as either retention in a COVID-19 emergency setting or transfer to tertiary hospital due to COVID-19 for patients allocated fluvoxamine versus placebo
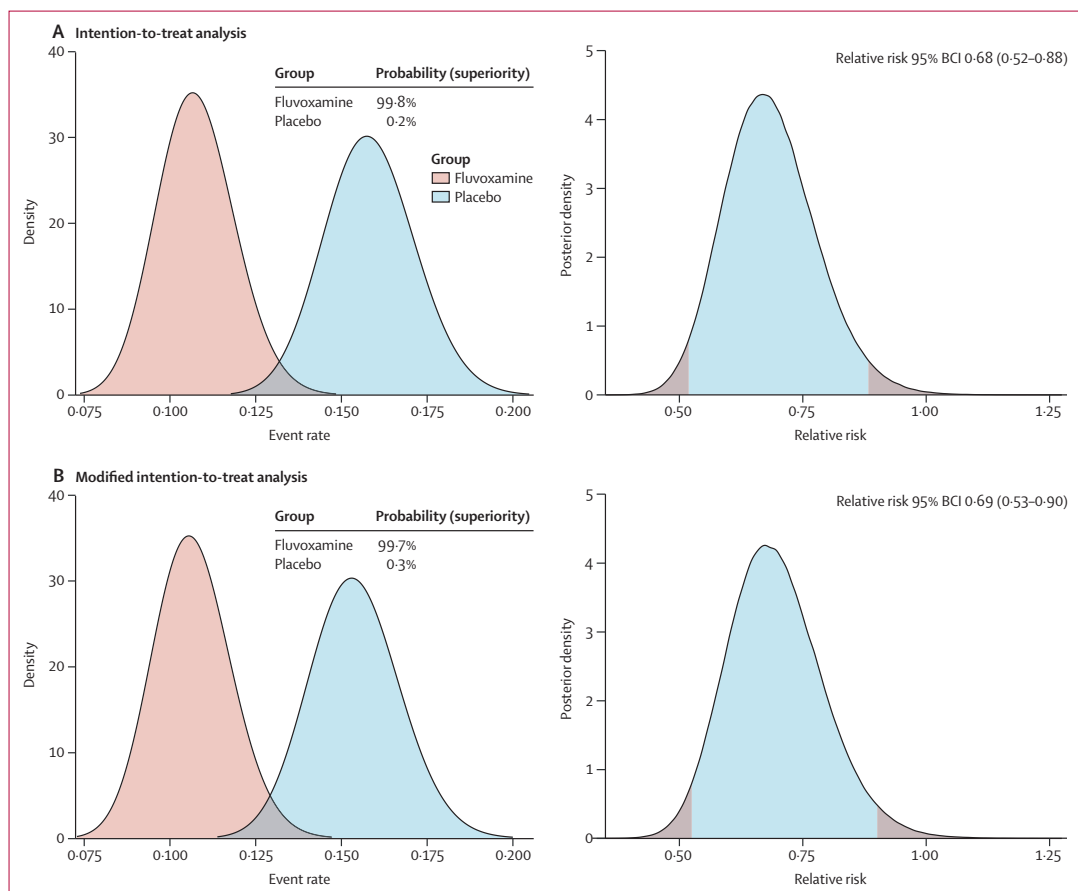

Figure 2: Probability of efficacy and Bayesian relative risk of hospitalisation defined as either retention in a COVID-19 emergency setting or transfer to tertiary hospital due to COVID-19 for fluvoxamine versus placebo
BCI=Bayesian credible interval.

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In the fluvoxamine group 79 (11%) participants had a primary outcome event compared with 119 (16%) in the placebo group (table 2). Most events (87%) were hospitalisations. On the basis of the Bayesian beta-binomial model, there was evidence of a benefit of fluvoxamine reducing the composite primary endpoint of hospitalisation defined as either retention in a COVID-19 emergency setting or transfer to tertiary hospital due to COVID-19 (RR 0·68; 95% Bayesian credible interval [BCI] 0·52–0·88) in the ITT population (figure 2A) and RR 0·69; 95% BCI 0·53–0·90 in a modified ITT population (figure 2B). The number needed to treat was 20. Per-protocol analysis showed a larger treatment effect (0·34, 95% BCI 0·21–0·54). The probability that the event rate was lower in the fluvoxamine group compared with placebo was 99·8% for the ITT population and 99·7% for the mITT population (figure 2A, B). When the DSMC met on Aug 5, 2021, it recommended that the TOGETHER trial stop randomly assigning patients to the fluvoxamine group, as this comparison had met the prespecified superiority criterion for the primary endpoint (pre-specified superiority threshold 97·6%).

Table 3 presents findings from secondary outcome analyses. There were no significant differences between fluvoxamine and placebo for viral clearance at day 7 (p=0·090) and hospitalisations due to COVID (p=0·10), all-cause hospitalisations (p=0·09), time to hospitalisation (p=0·11), number of days in hospital (p=0·06), mortality (p=0·24), time to death (p=0·49), number of days on mechanical ventilation (p=0·90), time to recovery (p=0·79) or the PROMIS Global Physical (p=0·55) or Mental Scale (p=0·32; appendix 2 p 8).

84 participants stopped fluvoxamine and 64 participants stopped placebo owing to issues of tolerability. Per-protocol findings among patients who reported optimal adherence (greater than 80% for possible days) indicated a significant treatment effect (RR 0·34; 95% BCI 0·21–0·54 for the primary outcome and for mortality (odds ratio 0·09; 95% CI 0·01–0·47). With respect to adverse events, there were no significant differences in number of treatment emergent adverse events among patients in the fluvoxamine and placebo groups.

In the prespecified subgroup analysis, we found no evidence of moderation of treatment effect for fluvoxamine compared with placebo, for subgroups of age, sex, days since symptom onset, smoking status, or comorbidities (figure 3, appendix 2 p 9).

Discussion

This is, to the best of our knowledge, the first large, randomised controlled trial to test the efficacy of fluvoxamine for acute treatment of COVID-19. We found a clinically important absolute risk reduction of 5·0%, and 32% RR reduction, on the primary outcome of hospitalisation defined as either retention in a COVID-19 emergency setting or transfer to tertiary

	Fluvoxamine	Placebo	Estimated treatment effect (95% CI)	p value
Viral clearance (day 7)	40/207 (19%)	58/221 (26%)	0·67 (0·42–1·06)*	0·090
Hospitalised for COVID	75/741 (10%)	97/756 (13%)	0·77 (0·55–1·05)*	0·10
All-cause hospitalisation	76/741 (10%)	99/756 (13%)	0·76 (0·58–1·04)*	0·088
Time to hospitalisation, days	5 (3–7)	5 (3–7·5)	0·79 (0·58–1·06)†	0·11
Period of hospitalisation, days	8 (5–13)	6 (3–10·75)	1·23 (0·99–1·53)‡	0·059
Emergency setting visit for at least 6 h	7/741 (1%)	36/756 (5%)	0·19 (0·08–0·41)*	0·0001
Time to the emergency visit for at least 6 h, days	4 (3–7)	5 (3–8·25)	0·20 (0·09–0·44)†	0·002
Death, intention to treat	17/741 (2%)	25/756 (3%)	0·69 (0·36–1·27)*	0·24
Time to death, days	17 (9–21)	14 (8–20)	0·80 (0·43–1·51)†	0·49
Mechanical ventilation	26	34	0·77 (0·45–1·30)	0·33
Time on mechanical ventilator, days	5·5 (3–12·75)	6·5 (2·25–12)	1·03 (0·64–1·67)‡	0·90
Adherence	548/741 (74%)	618/738 (82%)	0·62 (0·48–0·47)*	0·0003
Death, per protocol	1/548 (<1%)	12/618 (2%)	0·09 (0·01–0·47)	0·022
Treatment emergent adverse event				
Grade 1	20/741 (3%)	11/756 (1%)	1·88 (0·91–4·09)*	0·096
Grade 2	72/741 (10%)	81/756 (11%)	0·91 (0·64–1·25)*	0·52
Grade 3	38/741 (5%)	50/756 (7%)	0·76 (0·49–1·18)*	0·22
Grade 4	21/741 (3%)	20/756 (3%)	1·07 (0·58–2·01)*	0·82
Grade 5	18/741 (2%)	26/756 (3%)	0·70 (0·37–1·28)*	0·25

Data are n/N (%) or median (IQR) unless otherwise stated. *Unadjusted odds ratio. †Unadjusted hazard ratio. ‡Exponentiated unadjusted estimates from a log-transformed linear regression.

Table 3: Secondary outcomes of fluvoxamine versus placebo in the TOGETHER trial

hospital due to COVID-19, consequent on the administration of fluvoxamine for 10 days. This study is only the second study to show an important treatment benefit for a repurposed drug in the early treatment population.[13] Our findings represent the complete analysis of the trial after the DSMC recommended stopping the active fluvoxamine group and all 28-day follow-up of randomly assigned patients. Given fluvoxamine's safety, tolerability, ease of use, low cost, and widespread availability, these findings might influence national and international guidelines on the clinical management of COVID-19.

Our results are consistent with an earlier smaller trial done in the USA (led by EJL and AMR).[6] That study used a higher dose of fluvoxamine (100 mg three times a day for 15 days) and included a lower risk group for the primary outcome but found no clinical deterioration among 80 patients receiving fluvoxamine versus six cases among 72 patients receiving placebo. A large observational study from France involved a different population, 7230 hospitalised COVID-19 patients, and reported a reduction in use of intubation or death with use of SSRIs.[5]

The underlying mechanism of fluvoxamine for COVID-19 disease remains uncertain. Although hypotheses include several potential mechanisms,[4] the main

Articles

	Placebo (n events)	Treatment (n events)		Hazard ratio (95% CI)	$p_{interaction}$
Age (years)					
≤50	379 (41)	368 (23)		0·57 (0·34–0·95)	0·60
>50	328 (72)	327 (50)		0·67 (0·47–0·96)	
Sex					
Female	453 (61)	409 (28)		0·49 (0·31–0·77)	0·10
Male	303 (58)	332 (51)		0·80 (0·55–1·16)	
Body-mass index (kg/m²)					
<30	373 (52)	355 (34)		0·67 (0·44–1·03)	0·87
≥30	375 (67)	376 (44)		0·64 (0·44–0·94)	
Time from onset of symptoms					
0–3 days	310 (39)	328 (30)		0·72 (0·45–1·15)	0·82
4–7 days	267 (44)	239 (31)		0·77 (0·49–1·23)	
Cardiovascular disease					
No	454 (60)	435 (39)		0·67 (0·45–1·00)	0·94
Yes	302 (59)	304 (40)		0·65 (0·44–0·97)	
Use of corticoid therapy					
No	747 (117)	733 (79)		0·67 (0·51–0·90)	0·53
Yes	8 (2)	4 (0)			
Chronic kidney disease					
No	702 (115)	704 (78)		0·66 (0·50–0·88)	0·60
Yes	54 (4)	35 (1)		0·37 (0·04–3·35)	
Smoking status					
Current	64 (5)	47 (3)		0·80 (0·19–3·33)	0·60
Former	89 (17)	107 (10)		0·46 (0·21–1·00)	
Never	601 (97)	586 (66)		0·69 (0·50–0·94)	

0·35   0·50   0·75   1·0   1·5

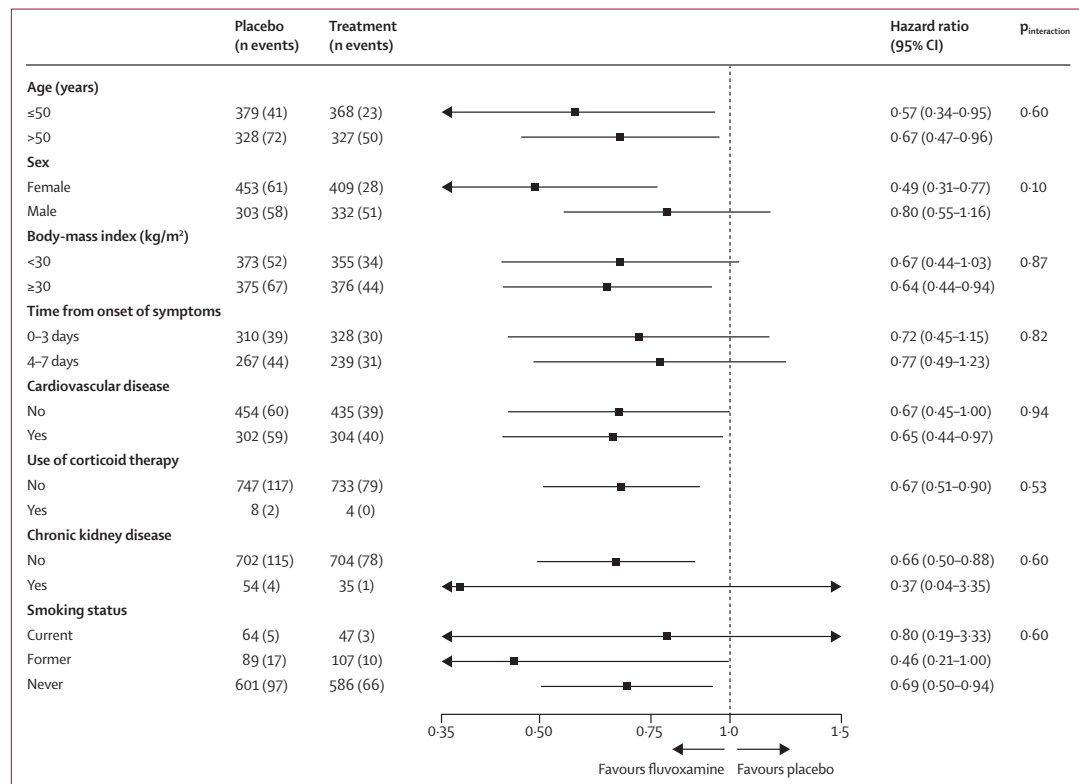← Favours fluvoxamine   Favours placebo →

Figure 3: Subgroup analyses of fluvoxamine versus placebo in the TOGETHER Trial

reason for the initial study of fluvoxamine as a treatment of COVID-19 was its anti-inflammatory action through activation of the S1R.[14] S1R is an endoplasmic reticulum (ER) chaperone membrane protein involved in many cellular functions,[15] including regulation of ER stress response–unfolded protein response and regulation of cytokine production in response to inflammatory triggers.[16] In the presence of fluvoxamine, S1R might prevent the ER stress sensor inositol-requiring enzyme 1α from splicing and activating the mRNA of X-box protein 1, a key regulator of cytokine production including interleukins IL-6, IL-8, IL-1β, and IL-12. In a 2019 study by Rosen and colleagues, fluvoxamine showed benefit in preclinical models of inflammation and sepsis through this mechanism.[16]

A second mechanism might be fluvoxamine's antiplatelet activity.[17] SSRIs can prevent loading of serotonin into platelets and inhibit platelet activation, which might reduce the risk of thrombosis, and these antiplatelet effects can be cardioprotective. Finally, another potential mechanism of action might be related to the effect of fluvoxamine in increasing plasma levels of melatonin.[16] In vitro and animal studies are needed to help clarify the most probable mechanism(s). Biomarker studies included as part of future randomised controlled trials might also help to clarify mechanisms.

Since the start of the COVID-19 pandemic, there have been more than 2800 randomised controlled trials registered on ClinicalTrials.gov. However, fewer than 300 have been reported and most clinical trials have been small and underpowered, with sample sizes less than 100. In many cases, these trials have been unsuccessful at recruiting as the local epidemics occur in waves and sustainable infrastructure to maintain staff or local interest for recruitment is lacking. The trials that provide the clearest medical understanding tend to be the larger platform trials, such as SOLIDARITY,[17] RECOVERY,[18] PRINCIPLE,[11] and REMAP-CAP.[19] As a result, we actively collaborate with other investigators running trials with overlapping interventions so that they can be aware of our study decisions and establish whether they should influence their respective trials.

Strengths of our trial include the rapid recruitment and enrolment of high-risk patients for the development of severe COVID-19. Our recruitment strategy involves engagement with the local public health system, thus allowing recruitment that frequently exceeds 20 patients per day. We enrolled only participants with diagnosed COVID-19 and less than 7 days of symptom onset using a commercially available COVID-19 rapid antigen test (Panbio, Abbott Rapid Diagnostics Jena, Jena, Germany).

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The concordance of COVID-19 positive tests with RT-PCR was evaluated on the group of participants with PCR evaluations and a concordance rate of greater than 99% on both tests collected at baseline was found. In this trial we did not enrol participants without positive COVID-19 tests, nor those who were asymptomatic SARS-CoV-2 positive. Our primary outcome is hospitalisation defined as either retention in a COVID-19 emergency setting for more than 6 h or transfer to tertiary hospital due to COVID-19. The event adjudication committee did count patient wait times as contributing to a primary endpoint. Specialised emergency settings were developed to respond to the Brazilian epidemic and we considered prolonged observation and treatment in these settings as equivalent in importance to hospitalisation as many patients who typically would be hospitalised were prevented from doing so owing to hospital over-capacity. In our trial, 87% of all primary outcome events eventually resulted in transfer to a tertiary hospital. Patients observed in both the emergency setting and hospital were counted only once. Our sub-group analyses examined pre-determined population groups and tests for interaction did not detect differing effects for any sub-group. Female sex was identified as a signficant sub-group favouring fluvoxamine while male sex was not, however we did not detect differing effects between the groups.

Our understanding of the epidemiology of COVID-19 as well as its disease progression and outcomes have evolved since beginning this platform trial in June, 2020. Early studies assessed the effects of interventions on viral load and clearance, whereas later studies also evaluate more clinical outcomes. We made adjustments to the trial according to prespecified rules and in communication with the appropriate ethics review committees that allowed us to respond to the epidemic waves while maintaining high rates of recruitment. Unlike many outpatient clinical trials, our study involves direct patient contact through the use of medical students, nurses, and physicians who do at-home visits as well as follow-up via telecommunications. Given the rapid recruitment of patients in combination with the high event rate of COVID-19 emergency setting visits and hospitalisations, we were able to evaluate the effects of interventions when portions of the planned population had been recruited. The period between first recruitment of a patient on fluvoxamine and the final data cut for our trial was 219 days.

Major limitations of our trial are related to the challenges of doing a trial in a disease that is not well characterised. There is no standard of care that exists for early treatment of COVID-19 and various advocacy groups promote different interventions, including some of those evaluated in this and our previous trials.[20] Furthermore, there is little understanding of who is at greatest risk of disease progression from this disease as some patients with numerous risk factors do recover quickly whereas some others with less established risk factors might not. Our population had a higher rate of hospitalisation events than observed in most clinical trials,[20] thus permitting inferences on treatment effects in this higher-risk population. Although intention-to-treat analysis provides more real-world evidence than per-protocol analysis, we found that patients who reported optimal adherence (greater than 80% for possible days—our per-protocol analysis) had a greater treatment benefit, suggesting that intensifying adherence to treatment might have considerable clinical benefits. However, adherence might be related to tolerability. 84 participants stopped fluvoxamine and 64 participants stopped in the placebo group for this reason. Finally, when the trial began, vaccines were not available in Brazil but became more widely available as the trial progressed. Although we modified inclusion criteria and permitted vaccinated patients during the trial, we believe this had minimal effect on the primary outcome as only 86 (6%) of 1497 reported at least one dose of a COVID-19 vaccine at the end of the trial.

Our trial has found that fluvoxamine, an inexpensive existing drug, reduces the need for advanced disease care in this high-risk population. A 10-day course of fluvoxamine costs approximately US$4 even in well-resourced settings.[21] Our study compares favourably with the treatment effects of more expensive treatments including monoclonal antibodies for outpatient treatment.[20,22,23] The absolute number of serious adverse events associated with fluvoxamine was lower than for placebo and this might reflect the modulatory effect of fluvoxamine on systemic inflammation in these participants. Lower respiratory tract infections were reported less frequently in patients in the fluvoxamine group than those in the placebo group. This is concordant with the reduction of hospital admissions in patients with confirmed COVID-19 treated with fluvoxamine, and the numerically lower number of patients requiring mechanical ventilation.

Fluvoxamine is widely available but is not on the WHO Essential Medicines List,[24] whereas a closely related SSRI, fluoxetine, is on the list. It is now crucial to establish whether a class effect exists and whehese drugs can be used interchangeably for COVID-19. The important findings that inhaled budesonide decreased time to recovery[11] among a similar population to our trial and had a trend towards decreased hospitalisations suggests that this as an alternative or additional intervention for outpatient care that should be evaluated. The PRINCIPLE trial evaluated time to recovery by means of self-reported recovery up to 28 days after randomisation to budesonide.[11] Our trial differed as we evaluated improvement in the WHO categorisation of disease disability up to days 14 and then 28 (appendix 2 p 7). Finally, our study was among primarily unvaccinated patients. Further evidence of treatment benefits are needed to establish the effect of fluvoxamine among vaccinated populations.

Use of interventions, including fluvoxamine, to prevent progression of illness and hospitalisation is critically

dependent on identifying higher-risk individuals. Unselected populations will have a lower risk. What absolute reduction in risk of clinical deterioration would motivate patients to choose treatment (probably the approximately 5% that we observed, but perhaps not much lower) remains uncertain. These considerations raise the importance of the development of a validated prediction rule for deterioration in patients in the early stages of COVID-19 infection.

Contributors

EJM and GR decided to publish the paper. EJM, GR, EAdSM-S, DCMS, LT, TSF, CVQdS, VHdSC, AMRN, APFGA, EDC, ADdFN, LCMS, MICS, LBR, RO, OH, JIF, HR, SS, PM, AVG, CRR, EJL, AMR, and GHG contributed to trial design. EJM, GR, JIF, EASdMS, DCMS, LT, TSF, CVQdS, VHdSC, AMRN, APFGA, EDC, ADdFN, LCMS, MICS, LBR, RO, OH, JIF, HR, SS, PM, AVG, CRR, EJL, and AMR helped plan the trial and ongoing recruitment. GR, EJM, EAdSMS, ACM, and DCMS were responsible for acquisition of data. EJM, GR, JIF, OH, HR, PM, SS, RO, CRR, LT, ACM, and GHG drafted the manuscript. OH, HR, and EJM contributed to the statistical analysis. GR and EJM had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors critically revised the manuscript. The members of the TOGETHER investigators group and their roles in the conduct of the trial are listed in appendix 2 (pp 2–4). All authors had full access to all the data in the study and take final responsibility for the decision to submit for publication. EJM and GR accessed and verified the underlying data.

Declaration of interests

EJM, AVG, SS, PM, and JIF have been employed by Platform Life Sciences. EJM, JIF, OH, and HR have been employed by Cytel. CRR has been employed by Certara. GR has been employed by Cardresearch. AMR and EJL are co-inventors on a patent application filed by Washington University for methods of treating COVID-19. All other authors declare no competing interests.

Data sharing

Data from the TOGETHER trial will be made available following publication of this manuscript to interested investigators through the International COVID-19 Data Alliance after accreditation and approval by the TOGETHER trial principal investigators (EJM and GR). Other study related documents can be found in the Open Science Framework.

Acknowledgments

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Supplementary appendix 1

This translation in Portuguese was submitted by the authors and we reproduce it as supplied. It has not been peer reviewed. The Lancet's editorial processes have only been applied to the original in English, which should serve as reference for this manuscript.

Esta tradução em português foi submetida pelos autores e nós não fizemos quaisquer alterações. Esta versão não foi revista por pares. O processo editorial do The Lancet só foi aplicado à versão original em inglês, que deve servir como referência para este artigo.

Fundamentos As evidências recentes indicam um potencial papel terapêutico da fluvoxamina para a COVID-19. No ensaio clínico TOGETHER para pacientes agudamente sintomáticos com COVID-19, objetivamos avaliar a eficácia da fluvoxamina versus placebo na prevenção da hospitalização definida como retenção em um ambiente de emergência COVID-19 > 06 hs ou transferência para um hospital terciário devido à COVID-19.

Métodos Este ensaio clínico randomizado e placebo controlado, em plataforma adaptativa, realizado em adultos brasileiros sintomáticos de alto risco, com teste positivo para a SARS-CoV-2, incluiu participantes elegíveis de 11 centros clínicos no Brasil, com um fator de risco conhecido para a progressão para doença grave. Os doentes foram aleatoriamente atribuídos (1:1) quer para a fluvoxamina (100 mg duas vezes por dia durante 10 dias) ou placebo (ou outros grupos de tratamento não reportados aqui). A equipe do estudo, o pessoal do centro e os pacientes não tinham conhecimento acerca da alocação do tratamento. Nosso desfecho primário foi um desfecho composto de hospitalização definido como retenção em um ambiente de emergência COVID-19 ou transferência para um hospital terciário devido a COVID-19 até 28 dias após a randomização com base na intenção de tratamento. A intenção modificada de tratar pacientes explorados que receberam pelo menos 24 h de tratamento antes de um evento de desfecho primário e a análise por protocolo explorou pacientes com um alto nível de adesão (>80%). Utilizamos uma estrutura analítica Bayesiana para estabelecer os efeitos juntamente com a probabilidade de sucesso da intervenção em comparação com placebo. O estudo é registrado no clinicaltrials.gov (NCT04727424) e está em andamento.

Resultados A equipe do estudo selecionou 9803 participantes potenciais para este ensaio clínico. O ensaio clínico foi iniciado em 2 de junho de 2020, e o protocolo atual com o braço de randomização para fluvoxamina de 20 de janeiro de 2021 a 5 de agosto de 2021, quando este foi interrompido por superioridade. 741 pacientes foram alocados para a fluvoxamina e 756 para o placebo. A idade média dos participantes foi de 50 anos (variação de 18-102 anos); 58% eram do sexo feminino. A proporção de pacientes observados em um ambiente de emergência COVID-19 por mais de 6 h ou transferidos para um hospital terciário devido à COVID-19 foi menor para o grupo da fluvoxamina em comparação ao placebo (79 [11%] de 741 vs 119 [16%] de 756); risco relativo [RR] 0.68; 95% intervalo de confiança Bayesiana [95% BCI]: 0.52-0.88), com uma probabilidade de superioridade de 99.8%, ultrapassando o limiar de superioridade pré estabelecido de 97.6% (diferença de risco de 5.0%). Considerando o desfecho primário observado, 87% foram hospitalizações. Os resultados para o desfecho primário foram semelhantes para a análise de intenção de tratamento modificada (RR 0.69, 95% BCI 0.53-0.90) e maiores na análise por protocolo (RR 0.34, 95% BCI, 0.21-0.54). Houve 17 óbitos no grupo da fluvoxamina e 25 óbitos no grupo do placebo na análise primária de intenção de tratamento (odds ratio [OR] 0.68, 95% CI: 0.36-1.27). Houve um óbito no grupo da fluvoxamina e 12 no grupo do placebo para a população por protocolo (OR 0.09; IC 95% 0.01-0.47). Não encontramos diferenças significativas no número de eventos adversos associados ao tratamento entre os pacientes do grupo da fluvoxamina e placebo.

Interpretação O tratamento com fluvoxamina (100 mg duas vezes por dia durante 10 dias) entre pacientes ambulatoriais de alto risco e com diagnóstico recente de COVID-19 reduziu a necessidade de hospitalização definida como retenção em uma unidade de emergência ou a transferência para uma internação de retaguarda.

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Supplementary appendix 2

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplementary web-Appendix

This appendix forms part of the original submission to:

Reis G, Silva EASM, Silva DCM et al: Effect of Early Treatment with Fluvoxamine on Risk of Emergency Care and Hospitalization Among Patients with COVID-19: The TOGETHER Randomized Platform Clinical Trial

1

Trial Infrastructure and the Extended TOGETHER investigators

The COVID-19 TOGETHER Trial initiative was designed to evaluate repurposed treatments for COVID-19 disease through an adaptive trial design in two arms being conducted in Brazil. The trial is supported by a network of primary care research centers located in the state of Minas Gerais, Brazil, devoted to a comprehensive evaluation and treatment of patients with COVID-19. The trial was fully integrated with local public health authorities (Brazilian Unified Health System – SUS) as part of coping strategy for COVID-19 pandemic. Namely, the main institutions involved were: Cardresearch – Cardiologia Assistencial e de Pesquisa. This initiative is funded by FastGrants and The Rainwater Foundation.

Brazilian Executive Committee

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Data Safety and Monitoring Committee

William Cameron, University of Ottawa (Canada), James Orbinski, York University (Canada), Sonal Singh, University of Massachusetts (USA), Kristian Thorlund, McMaster University (Canada), Jonas Haggstrom of Cytel Inc. (Sweden).

Clinical Events Classification Committee

Gilmar Reis[1,2] (chair), Luciene B Ribeiro[1] (adjudicator), Thiago S Ferreira[1] (adjudicator), Ana MR Nogueira (adjudicator)[1], Laura C Oliveira[1] (operations manager), Heloísa A Costa[1] (operations manager)

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2

manager), Carla SO França[1] (data management), Aline C Milagres[1] (data management), Luciene B Ribeiro[1] (regulatory affairs manager), Tainara S Vieira[1] (regulatory affairs), Lineria HM Suterio[1] (pharmaceutical operations manager)

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Participating Enrolling Centres
Included below are representatives from the enrolling centres at participating cities that enrolled at least 1 patient. Centres are listed in order of enrolment contribution. All study
sites were located in the State of Minas Gerais, Brazil.

Cardresearch – Cardiologia Assistencial e de Pesquisa

Aline Lúcia de Jesus Martins, Anna Clara de Jesus Oliveira, Bárbara Nogueira Roberti, Carina Daniela Lira Moreira Figueiredo, Carolina Couto de Azevedo Cysne, Clara Bensemann Gontijo Pereira, Daniela Carla Medeiros, Túlio Fonseca e Silva Quadros, Emanuelle Cristina Soares Gonçalves, Heloisa Alves Costa, João Victor Barbosa Silveira, Joselaine Gomes de Souza, Kênia Sthéfhane Guimarães Gonçalves, Laura Campos Oliveira, Letícia Campos Siqueira, Letícia de Fatimas Costa, Lorena Mesquita Alves, Luana Rosa Rodrigues, Lucas Júnio da Silva, Mariana Campos Siqueira, Marina Guimarães Bragatto, Rosemary Muniz de Oliveira, Stephanny Kelvyn Bessa, Tainara Silva Vieira, Tatiana Aparecida Gomes da Silva, Túlio Fonseca e Silva Quadros, Thais Campos Siqueira, Vânia Regina Carmo, Vitor Augusto Lima do Vale, Vitor Vilaça Oliveira.

City of Ibirité

Aline Cruz Milagres, Ana Carolina Aguiar Estevam, Ana Martins de Oliveira, André Henrique de Sousa Oliveira, Carla Stefany Oliveira França, Laylla Michelle Pereira, Luciléia Alcântara Gomes e Silva, Patrícia Santana Assis, Regiane Aparecida de Andrade, Thaís de Paula Ferreira da Silva, Thiago de Alcântara César

City of Sete Lagoas

Amanda Luiza do Espírito Santo Pinheiro, Ana Carolina Matos Ferreira, Ana Caroline Santos Silva, Ana Luiza Silva Taveira, Bruno Victor de Souza Lima, Débora Siqueira Diana, Emanuela Pontes Pereira Silveira, Francisca Lina Campos Gonçalves, Gabriel Corrêa Costa, Geraldo César Barroso de Souza, Guilherme Aurelio D'Oliveira Alves, Isadora Luiza Teixeira Neto, Jordanna Porto Inácio, Lara Silveira Marques, Larissa Martins do Nascimento, Larissa Oliveira Moreira, Lorena Luiza Soares de Oliveira, Lucas Eduardo Lessa Mussi, Lucas Medeiros Ruas, Luiza Nogueira Assis Barbosa, Marcelo Rodrigues da Costa Fernandes, Maria Eduarda Guimarães de Souza, Maria Thereza Figueiredo Bélem Calazans, Mariana Rodrigues Marinho de Bastos, Pedro Henrique Arcanjo Alvarenga, Quimberli Vassinave Cujuí, Vinicius Alves Correa, Vitória Aparecida Cunha, Viviane Costa Santos

City of Governador Valadares

Adriana Marcos Mendes Rabelo, Aline do Carmo Rosa , Ana Paula Vilas Boas Wherberth, Arthur Henrique Nunes Leite Oliveira, Damiana Rogai Siqueira, Felipe Coelho Soares de Oliveira, Felipe Fraga Damaceno, Guilherme Rhis, Iandra Silva Almeida, Igor Barros de Araújo Borges, Igor Brandão Rocha, Jorge Carlos do Amaral Júnior, José Pio Marques II, Laura Lima Vargas, Luiz Eduardo Coelho Fava, Marina Lacerda Marques, Maura Alina Morais Veríssimo, Neila Rodrigues

Vargas de Paula, Pâmela de Sousa Dias Demuner, Rafaella Rosa de Oliveira Fernandes, Ramail Santos Pouzas, Roberta Coelho de Marco, Ronan Figueiredo Mourão, Sabrina Stefany da Silva Souza, Sara Silva Ferraz

City of Brumadinho

Ana Beatriz Amorim, Carolina Francisca Martins, Huisnei Ferreira Lourenço, Jussara Carolina Assis Ribeiro Nascimento, Solange Santos Moreira Sales

City of Nova Lima

Leticia de Fatima Costa, Maria do Carmo, Fernanda Freitas Pinheiro, Felipe Viana Santos

Public health authorities and mayors
We are in debt with the following local public health authorities and mayors (listed by enrollment):

City of Sete Lagoas
Duílio de Castro (Mayor), Flávio Pimenta Silveira (public health authority), Alber Alípio Ribeiro (public health authority)

City of Montes Claros
Humberto Guimarães Souto (Mayor), Dulce Pimenta Gonçalves (public health authority)

City of Governador Valadares
André Luiz Coelho Merlo (Mayor), Edna Gomes Leite (public health authority)

City of Ibirité
William Parreira Duarte (Mayor), Carina Bitarães (public health authority)

City of Brumadinho
Avimar de Melo Barcelos (Mayor), Eduardo Diniz Callegari (public health authority)

City of Nova Lima
João Marcelo Diegues Pereira (Mayor), Diogo Jonata Ribeiro (public health authority)

4

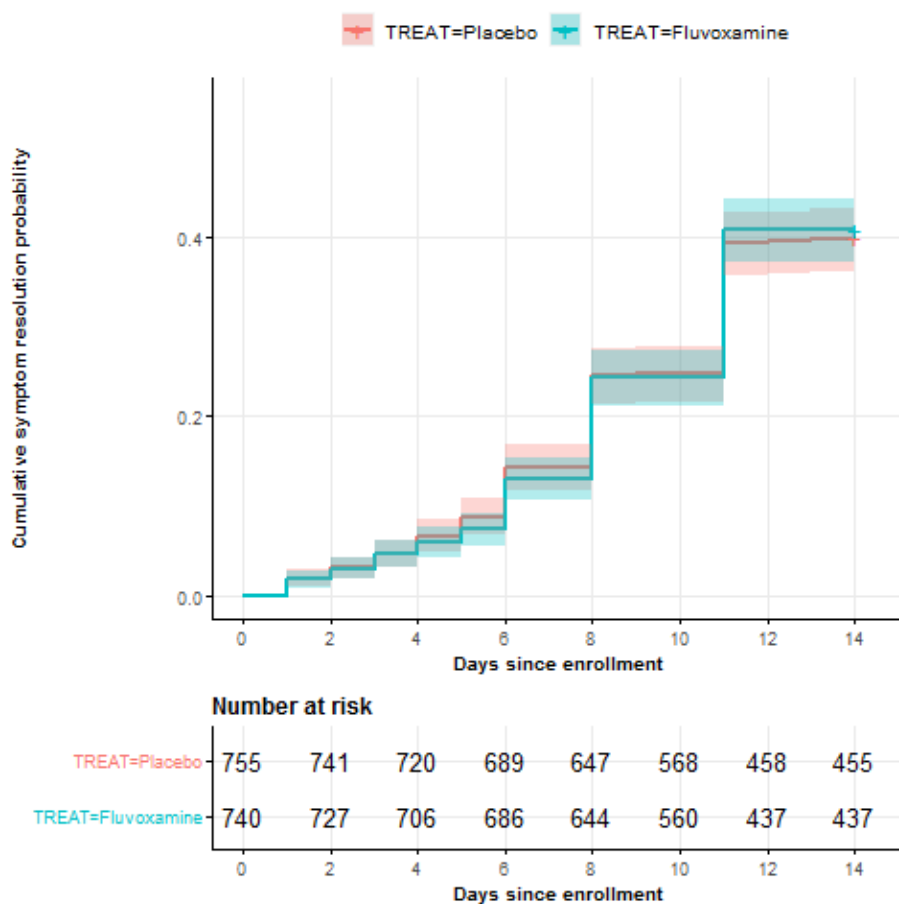**Supplementary Tables and Figures**

eFigure 1: Time to hospitalization or extended emergency room visit due to COVID-19

PTX0463 Page 19 of 23
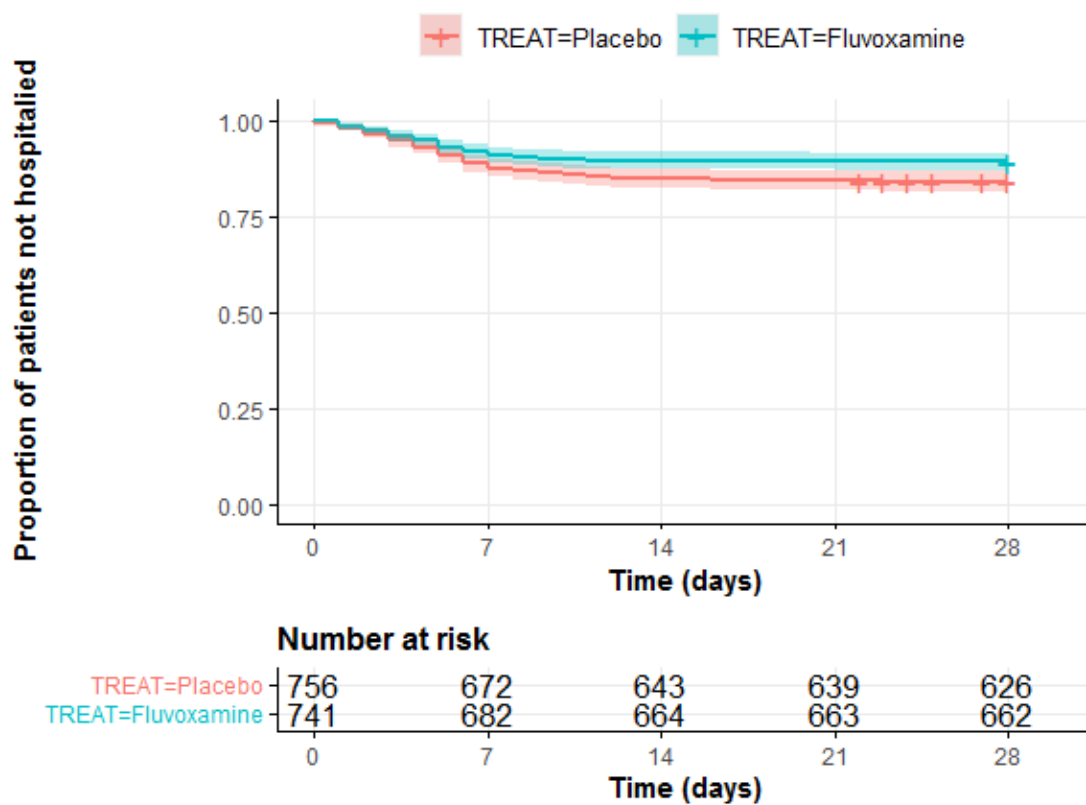
eFigure 2: Time to symptom resolution (WHO symptom index scale)

PTX0463 Page 20 of 23

eFigure3: Probability of viral detection (Days 0, 3, 7)

PTX0463 Page 21 of 23
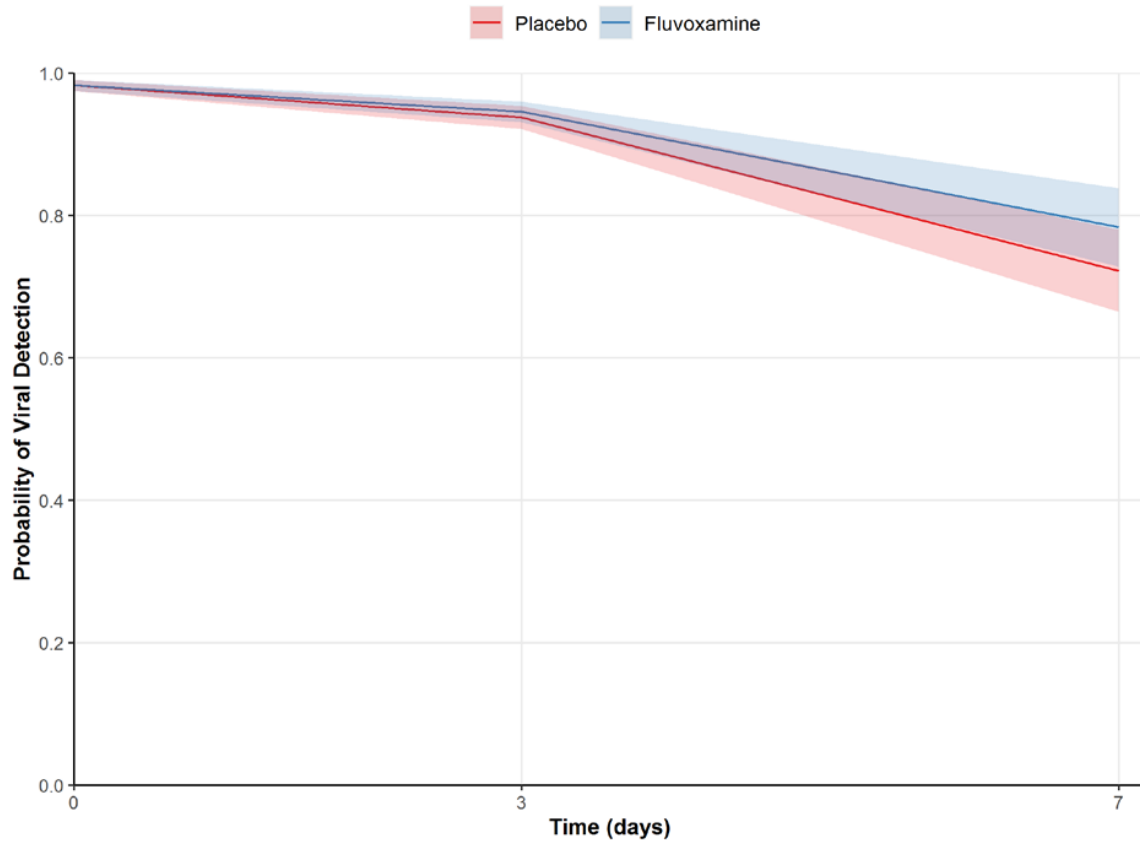
Factor	Subgroup	N_Placebo	N_Fluvoxamine	n_Placebo	n_Fluvoxamine	HR (95% CI)
Age	<=50	379	368	41	23	0.57 [0.34; 0.95]
Age	>50	328	327	72	50	0.67 [0.47; 0.96]
Sex	Female	453	409	61	28	0.49 [0.31; 0.77]
Sex	Male	303	332	58	51	0.80 [0.55; 1.16]
BMI (Kg/m^2)	<30	373	355	52	34	0.67 [0.44; 1.03]
BMI (Kg/m^2)	>30	375	376	67	44	0.64 [0.44; 0.94]
Time from onset of symptoms	0-3 days	310	328	39	30	0.72 [0.45; 1.15]
Time from onset of symptoms	4-7 days	267	239	44	31	0.77 [0.49; 1.23]
Cardiovascular disease	N	747	733	117	79	0.67 [0.51; 0.90]
Cardiovascular disease	Y	8	4	2	0	
Chronic kidney disease	N	702	704	115	78	0.66 [0.50; 0.88]
Chronic kidney disease	Y	54	35	4	1	0.37 [0.04; 3.35]
Smoking status	Current	64	47	5	3	0.80 [0.19; 3.33]
Smoking status	Former	89	107	17	10	0.46 [0.21; 1.00]

9

| Smoking status | Never | 601 | 586 | 97 | 66 | 0.69 [0.50; 0.94] |

eTable1: Summary of Sub-Group Analysis for Hospitalization or Extended Emergency Room Visit Due to COVID-19

10

EXHIBIT B

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

GENENTECH, INC. and
INTERMUNE, INC.,

      Plaintiffs,

      v.

APOTEX INC., et al.,

      Defendants.

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)
)
)
)
)
)
)
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)
)

C.A. No. 19-78 (RGA)
CONSOLIDATED

SECOND SUPPLEMENTAL EXPERT REPORT OF STEVEN D. NATHAN, M.D.

1.   I have been retained by Loeb & Loeb LLP on behalf of Plaintiffs Genentech, Inc.

and InterMune, Inc. (collectively, "InterMune") to provide my opinions related to certain issues

in connection with the patents and their respective asserted claims listed in Appendix D attached

to my Opening and Supplemental Reports ("the InterMune patents").

2.   This Second Supplemental Report further supplements my February 17, 2021,

Opening Report, May 12, 2021, Supplemental Report, and June 18, 2021 Reply Report, based on

information that was not available to me when I submitted those reports and only became

available to me and to the public on October 27, 2021. I rely on my three aforementioned expert

reports and incorporate them by reference, in their entirety including the Appendices therein.

3.   In addition to the InterMune Patents and the exhibits cited in this Second

Supplemental Report, as well as in my Opening, Supplemental, and Reply Reports, I have

considered Gilmar Reis et al., *Effect of Early Treatment with Fluvoxamine on Risk of Emergency*

Care and Hospitalisation among Patients with COVID-19: the TOGETHER Randomised,

Platform Clinical Trial, Lancet Global Health, *available at*

https://www.thelancet.com/action/showPdf?pii=S2214-109X%2821%2900448-4 (last visited

Oct. 28, 2021) [PTX0463] ("Reis et al."). I have also relied upon my decades of experience,

including my extensive clinical experience specifically in the fields of pulmonary and critical

care medicine, and in treating patients suffering from respiratory diseases, including IPF. My

knowledge is further reinforced from having read, authored and co-authored many publications

in this area, and my general experience.

4.   The Reis et al. article reports the results of "the first large, randomised controlled

trial to test the efficacy of fluvoxamine for acute treatment of COVID-19." Reis et al. at 7. In

this phase 3 study, 741 patients received fluvoxamine and 756 patients received placebo. *See id.*

at 1. Compared with placebo, patients receiving fluvoxamine had a lower risk of hospitalization.

Id. at 2. The authors concluded that the "[r]esults provide compelling evidence of fluvoxamine's

benefit in reducing acute morbidity from COVID-19 illness." *Id.* They also noted that the

results "compare[] favourably with the treatment effects of more expensive treatments including

monoclonal antibodies for outpatient treatment." *Id*. at 9. Especially noteworthy is that in those

patients who took more than 80% of the prescribed dose of study drug, there were twelve deaths

in the placebo arm versus only one in the fluvoxamine arm of the study. I believe that physicians

will find this data to be quite compelling which will lead to more off-label prescriptions of

fluvoxamine.

   5. The findings reported in the Reis et al. article provide further support for my

opinions in paragraph 279 in my Supplemental Report and paragraph 63 and footnote 6 of my

Reply Report. The emerging positive results provide additional support for my opinion that

fluvoxamine would be a potential treatment for IPF patients who are receiving pirfenidone and

who develop COVID. These patients are at great risk from COVID, due to their diminished lung

reserve, and it is likely that physicians are going to be aggressive in trying to treat them with

available "repurposed" drugs such as fluvoxamine, especially given the efficacy as

demonstrated in the recent article by Reis et al. The willingness of physicians to prescribe

available drugs for COVID has been demonstrated by the widespread off label use of drugs such

as hydroxychloroquine and ivermectin for COVID treatment for which there is no demonstrable

efficacy based on the body of evidence in the literature.

   6. For IPF patients taking pirfenidone being treated with fluvoxamine for COVID, I

would follow the pirfenidone label and modify pirfenidone dosages for those patients while they

are also on fluvoxamine. Accordingly, based on the emerging positive clinical data, at least

some physicians will use fluvoxamine for the treatment of COVID, including in IPF patients

receiving pirfenidone, and will modify treatment pursuant to the instructions in the labeling, thus

practicing the claimed methods.

I declare under penalty of perjury that the foregoing is true and correct to the best of my

own personal knowledge.

Executed on _____October 29, 2021_____, at _____.

Steven Nathan
_____

Steven D. Nathan, M.D.

3

EXHIBIT C

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

GENENTECH, INC. and INTERMUNE, INC.,	)))	C.A. No. 19-78 (RGA) CONSOLIDATED
Plaintiffs,	)))	
v.	))	**CONTAINS HIGHLY CONFIDENTIAL INFORMATION**
AUROBINDO PHARMA LIMITED, et al.,	)))	
Defendants.	))	

SUPPLEMENTAL EXPERT REPORT OF STEVEN D. NATHAN, M.D.

additional in vivo studies based on the teachings of the Pirespa Label 2008 and Deliberation

Results.

277.   Indeed, my interpretation of the Pirespa Label 2008 and the Deliberation Results

is consistent with the Patent Examiner's interpretation. In the '002 patent Examiner's Statement

of Reasons for Allowance, the Patent Examiner concluded that

> Shionogi & Co. teach that pirfenidone is metabolized by multiple CYP molecular
> species in the human liver including CYPA12, 2C9, 2C19, 2D6, and 2E1. Thus,
> Shionogi & Co. also teach that it is estimated that pirfenidone is insusceptible to
> CYP inhibition by other drugs since multiple CYP molecules are involved in the
> metabolism reaction. Shionogi & Co. does not teach dose reduction of pirfenidone
> when administered concurrently with fluvoxamine.

'002 patent Reasons for Allowance, at 3-4. Thus, a POSA would not have expected a drug-drug

interaction between pirfenidone and a CYP1A2 inhibitor, such as fluvoxamine. In addition, the

Pirespa Label 2008 and the Deliberation Results do not say anything about dose adjustment to

mitigate the drug-drug interaction.

C.   There Are Substantial Differences Between The Prior Art and The Claimed Inventions

278.   I briefly reviewed InterMune's clinical testing of these inventions in the section

above concerning enablement, and incorporate that discussion by reference for this discussion.

279.   I also reviewed the asserted claims in Appendix D. Briefly, asserted claims 3 and

9 in the '002 patent provide specific pirfenidone dosing instructions when co-administering

pirfenidone with fluvoxamine that are based on the clinical test results obtained by InterMune

and disclosed in these patents. Dr. Duncan suggests (see, e.g., Duncan Report, ¶ 186) that there

may be alternative treatments for obsessive compulsive disorder, for which fluvoxamine is

indicated. However, without the knowledge of the Intermune patent, a POSA would not know

about the DDI and would not consider prescribing another agent (if indeed one was regarded as

equivalent to fluvoxamine). In addition, fluvoxamine, is being tested as a potential COVID-19

therapy and could be used off-label in this and perhaps other regards in the future[7]. Therefore, claims 3 and 9 in the '002 patent cover a potentially important concomitant administration method for treating IPF patients with pirfenidone who might also benefit from taking fluvoxamine. Other asserted claims provide for discontinuing co-administration of fluvoxamine and/or certain other strong CYP1A2 inhibitors.

280.   As I explained above, a POSA would have followed the Pirespa Label 2008 and prescribed pirfenidone to patients who were on CYP1A2 inhibitors, such as fluvoxamine or ciprofloxacin (which I discuss in the next section), without instructing the patients to discontinue the CYP1A2 inhibitors or reduce the dose of pirfenidone.

281.   In contrast, InterMune's data demonstrates that patients who take pirfenidone with CYP1A2 inhibitors would have been overexposed to pirfenidone. For example, InterMune has shown that fluvoxamine, which is a strong CYP1A2 inhibitor, would increase the exposure of pirfenidone by 6-fold, which is substantial. Such overexposure would lead to great risks of adverse events. And based on the fact that pirfenidone is hepatotoxic, a six-fold increase in pirfenidone exposure would have undoubtedly led to adverse events, including but not limited to, potentially significant liver toxicity.

D.   The Asserted Claims Of The '002, '383, '610, and '780 Patents Would Not Have Been Obvious

282.   For all the foregoing reasons, I disagree with Dr. Duncan's conclusions that asserted claims in the '002, '383, '610, and '780 patents would have been obvious. Based on the

---

[7] *See*, Lenze et al., *Fluvoxamine vs Placebo and Clinical Deterioration in Outpatients With Symptomatic COVID-19*, JAMA, 324(22): 2292-2300 (November 12, 2020); Hashimoto, *Repurposing of CNS drugs to treat COVID 19 infection: targeting the sigma 1 receptor*, European Archives of Psychiatry and Clinical Neuroscience (published online January 5, 2021); and NIH COVID-19 Treatment Guidelines, last updated April 23, 2021, available at https://www.covid19treatmentguidelines.nih.gov/immunomodulators/fluvoxamine/.

XVIII. DEMONSTRATIVE EXHIBITS TO SUMMARIZE AND/OR EXPLAIN OPINIONS

303.   I intend to use exhibits (including demonstrative exhibits I have not yet created) at

trial to summarize and illustrate my assertions and opinions including, among other things,

Plaintiffs documents, excerpts from depositions taken in this case and schematics and documents

produced by Defendants. In the event that additional information becomes available, I may

supplement this Supplemental Report to take into account such additional information.

304.   If it is helpful to the Court, I am ready to provide additional background

regarding, for example, FDA practices and procedures, discussed in this Supplemental Report.

I declare under penalty of perjury that the foregoing is true and correct to the best of my

own personal knowledge.

Executed on _____May 12, 2021_____ , at ___Inova Fairfax Hospital, 3300 Gallows Road, Falls Church VA 22042_____.

Dr. Steven Nathan
_____
Steven D. Nathan, M.D.

EXHIBIT D

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

GENENTECH, INC. and INTERMUNE, INC.,	)))	C.A. No. 19-78 (RGA) CONSOLIDATED
Plaintiffs,	)))	
v.	))	**CONTAINS HIGHLY CONFIDENTIAL INFORMATION**
AUROBINDO PHARMA LIMITED, et al.,	)))	
Defendants.	))	

REPLY EXPERT REPORT OF STEVEN D. NATHAN, M.D.

63.   In my practice, if an IPF patient were taking fluvoxamine, I would certainly have a conversation with the patient's psychiatrist and then come up with a game plan on a case-by-case basis[6]. Insofar as this would concern pirfenidone administration to treat IPF, that treatment plan would be based on the instructions in the pirfenidone label – either to discontinue fluvoxamine or reduce the dosage of pirfenidone – and taking into consideration individual patients' needs.

64.   As I explained in my Opening Report, Defendants' pirfenidone label instructs consumers of their generic pirfenidone products to discontinue fluvoxamine while taking pirfenidone or to reduce the dosage of pirfenidone if fluvoxamine cannot be avoided. *See, e.g*., my Opening Report Section XI, and App. D (*supra*). And Dr. Morrow does not deny this.

65.   Dr. Morrow further states that "Defendants have not provided specific instructions to follow the recited steps of the asserted claims." Morrow Rebuttal ¶ 100. I disagree. Defendants' proposed pirfenidone labels provide that Defendants' generic pirfenidone products are indicated for the treatment of IPF by administering pirfenidone. *See, e.g*., my Opening Report ¶ 85. I also explained that physicians would follow instructions of Defendants' pirfenidone label when a patient who needs pirfenidone is taking fluvoxamine or other CYP1A2 inhibitors, such as the instruction to discontinue fluvoxamine before administering pirfenidone or to reduce the dosage of pirfenidone when coadministering with fluvoxamine. *See id*. Section XI. And since the asserted claims read on Defendants' pirfenidone labels, it is my opinion that

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[6] In addition, fluvoxamine has been used for treating COVID in clinical trials. I would be very concerned if IPF patients who are receiving pirfenidone contracted COVID, because they are at great risk with their diminished lung reserve. In that scenario, fluvoxamine would be a potential treatment and I would follow the pirfenidone label and modify pirfenidone dosages for those patients while they are also on fluvoxamine. *See* my Supplemental Report ¶ 279 and references I cited in fn. 7 therein.

I declare under penalty of perjury that the foregoing is true and correct to the best of my

own personal knowledge.

Executed on _____June 18, 2021_____, at ___Steven Nathan_____.

Dr. Steven Nathan

_____

Steven D. Nathan, M.D.

EXHIBIT E

```
 1                 IN THE UNITED STATES DISTRICT COURT

 2                  FOR THE DISTRICT OF DELAWARE

 3

 4       --------------------------------x

 5       GENENTECH, INC. and INTERMUNE,   :

 6       INC.,                            :

 7                     Plaintiffs,        :   Case No.

 8            vs.                         :   19-78 (RGA)

 9       AUROBINDO PHARMA LIMITED, ET     :

10       AL.,                             :

11                     Defendants.        :

12       --------------------------------x

13

14               ::: HIGHLY CONFIDENTIAL :::

15

16        VIDEOTAPED DEPOSITION OF STEVEN NATHAN, M.D.

17                   CONDUCTED VIRTUALLY

18                 Friday, August 13, 2021

19

20

21

22       Stenographically Reported by:
         LORI STOKES
23       CSR No. 12732

24       Job No. 386934

25       Pages 1-279
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HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

Transcript of Steven Nathan, M.D.

Conducted on August 13, 2021   39

1	in the document that's been marked as Exhibit 1?	05:43:14
2	A No material changes. Just additions of	05:43:18
3	papers and talks that I might have given, but	05:43:21
4	nothing material.	05:43:25
5	Q Okay. Now, Dr. Nathan -- you can put	05:43:26
6	that document aside.	05:43:40
7	MR. MITROKOSTAS: And, Mr. Martin, you	05:43:43
8	can take it off the screen. Thank you.	05:43:49
9	BY MR. MITROKOSTAS:	05:43:51
10	Q Have you ever prescribed a drug called	05:43:53
11	fluvoxamine?	05:43:54
12	A I don't recall if I've prescribed it.	05:43:56
13	It's a psychiatric drug, and I don't prescribe	05:43:58
14	psychiatric drugs.	05:44:02
15	Q It's typically prescribed as an	05:44:03
16	antidepressant, correct?	05:44:06
17	A Yes.	05:44:09
18	Q Okay. And --	05:44:10
19	A To my knowledge.	05:44:10
20	Q Yes. And --	05:44:11
21	A Interestingly, it's also -- there's also	05:44:11
22	some data to suggest that it might be good for	05:44:13
23	COVID. So, you know, it's -- as with all drugs,	05:44:15
24	there can be evolving indications as well.	05:44:17
25	Q Right.	05:44:20

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER
Transcript of Steven Nathan, M.D.
Conducted on August 13, 2021   40

1	Well, fluvoxamine has not been approved	05:44:21
2	for the treatment of COVID, correct?	05:44:26
3	A It has not. But, you know, people are	05:44:29
4	using a lot of different drugs off-label for COVID.	05:44:31
5	Q Okay. And fluvoxamine is a -- as you	05:44:34
6	mentioned, a psychiatric drug, correct?	05:44:36
7	A To my understanding, yes.	05:44:39
8	Q Okay. And you don't prescribe	05:44:41
9	psychiatric drugs, correct?	05:44:43
10	A That's correct.	05:44:45
11	Q Right.	05:44:46
12	In fact, pulmonologists typically don't	05:44:46
13	prescribe psychiatric drugs for their patients,	05:44:50
14	correct?	05:44:50
15	A I can't answer for that.	05:44:50
16	MR. MacRAE: Object to the form of the	05:44:54
17	question.	05:44:55
18	You may answer.	05:44:55
19	THE WITNESS: I can't answer for that.	05:44:57
20	We work in a highly specialized clinic,	05:44:58
21	and we take care of patients with various forms of	05:45:01
22	advanced lung disease. Our expectation is that	05:45:01
23	patients have primary pulmonologists as well as	05:45:03
24	primary care physicians.	05:45:06
25	So there probably are pulmonologists who	05:45:07

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

Transcript of Steven Nathan, M.D.

Conducted on August 13, 2021   279
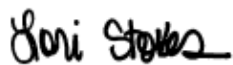
```
 1                          )
     STATE OF CALIFORNIA    )
 2                          )

 3                CERTIFICATE OF REPORTER

 4        I, LORI STOKES, do hereby certify that the

 5   witness in the foregoing deposition was by me duly

 6   affirmed to tell the truth, the whole truth and

 7   nothing but the truth in the within-entitled cause;

 8   that said deposition was taken at the time and

 9   place therein stated; that the testimony of said

10   witness was reported by me and was thereafter

11   transcribed under my direction and supervision;

12   that the foregoing is a full, complete and true

13   record of said testimony; that the witness was

14   given an opportunity to read and, if necessary,

15   correct said deposition and to subscribe the same.

16        I further certify that I am not of counsel or

17   attorney for either or any of the parties in the

18   foregoing deposition and caption named, or in any

19   way interested in the outcome of the cause named in

20   said caption.

21        IN WITNESS WHEREOF, I have hereunto set my

22   hand this 14th day of August, 2021.

23
                 Lori Stokes
24        _____

25           LORI STOKES, CSR No. 12732
```